UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,783	11/13/2001	Itamar Willner	10980-16001	8069

20985 7590 10/06/2004

FISH & RICHARDSON, PC
12390 EL CAMINO REAL
SAN DIEGO, CA 92130-2081

EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,783	WILLNER ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *9-22 and 34-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 23-31* is/are rejected.

7)☒ Claim(s) *32 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on April 5, 2004 has been entered. The claims pending in this application are claims 1-47. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn. Since newly submitted claims 46 and 47 contain the phrase "detecting the presence of said verification oligonucleotides on the sensing interface by measuring an increase in the mass immobilized on the sensing interface" and claims 1-9 and 23-33 that are examined does not have a limitation "detecting the presence of said verification oligonucleotides on the sensing interface by measuring an increase in the mass immobilized on the sensing interface", claims 46 and 47 are directed to an invention that is independent or distinct from the invention originally claimed. Since applicant has received an action on the merits for the originally presented invention, claims 46 and 47 are not considered to be original presentation for prosecution on the merits. Accordingly, claims 46 and 47 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Since claims 10-22 and 34-45 have been withdrawn due to restriction requirement and election species and amended claim 9 is dependent on claim 46 (non-elected invention), claims 1-9 and 23-33 will be examined.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. For example, see page 1 of the specification. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP

§ 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. Note that applicant does not address this issue.

Claim Objections

3. Claims 1 and 23 are objected to because of the following informality: "having each a nucleotide sequence" in steps a) and b) of the claims should be " wherein each capturing oligonucleotide has a nucleotide sequence" in order to make better English languages. Note that applicant does not address this issue.

4. Claims 3 and 28 are objected to because of the following informality: "stably hybridizing portion of the capturing and verification oligonucleotides is" should be "stably hybridizing portions of the capturing and verification oligonucleotides are".

5. Claim 4 is objected to because of the following informalities: (1) "the verification oligonucleotide is" should be "the verification oligonucleotides are" in order to correspond to verification oligonucleotides in claim 1; and (2) "step (e) of the method comprises" should be "step (e) is performed by".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To the extent that the claimed composition/or methods are not described in the instant disclosure, claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

The recitation "by measuring insulation of the sensing interface to interfacial electron transfer between the sensing interface and the surrounding medium" is added to the newly amended independent claim 1. Although the specification describes that the presence of the verification oligonucleotide on the sensing surface is based on measurement of changes in resonance frequency of the probe (e.g., see page 5, lines 18-22), the specification fails to define or provide any disclosure to support such claim recitation.

> MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.".

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 26 is rejected as vague and indefinite because it is unclear what kind of probe can be considered as a microbalance quartz-crystal probe. Do a microbalance quartz-crystal probe mean a probe immobilized on a quartz-crystal microbalance? Note that the specification does not define "a microbalance quartz-crystal probe". Please clarify.

Response to Arguments

In page 12, second paragraph of applicant's remarks, applicant argues that "the term 'microbalance quartz-crystal probe' in claim 26 is well known and understood by a person skilled in the art. For example, it may be an Au-quartz probe (see page 10, line 19). The Examiner is referred to page 2 of the specification, lines 16-21, and to the reference cited there (no. 11, Bardea, et al.), and also to page 6, lines 1-5, and to WO 97/04314 cited there, especially page 4, lines 19-24. Accordingly, there can be no doubt based upon the information available in the art that 'microbalance quartz-crystal probe' are well known and thus are not indefinite".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection since page 2 of the specification, lines 16-21, the reference from Bardea et al., (reference 11 of the specification) and page 4, lines 19-24 of WO 97/04314 do not define "microbalance quartz-crystal probe". Note that the rejection is based on microbalance quartz-crystal probe and is not based on quartz-crystal microbalance which is well known in the art.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1 and 2 are rejected under 35 U.S.C. 102(e) as being anticipated by Blackburn *et al.*, (US Patent No.6,686,150, priority date: January 29, 1998).

Blackburn *et al.*, teach a method for detecting a target sequence in a sample comprising: a) providing a rolling circle probe (RCP) comprising: i) a first ligation sequence substantially complementary to a first domain of said target sequence; ii) a second ligation sequence substantially complementary to a second domain of said target sequence; and iii) a priming sequence; b) hybridizing said first ligation sequence to said first domain and said second ligation sequence to said second domain to form a first hybridization complex; c) ligating said first and second ligation sequences together; d) adding to said first hybridization complex: i) a primer substantially complementary to said priming sequence; ii) a polymerase; iii) dNTPs; and iv) an electron transfer moiety (ETM); to form a rolling circle concatamer comprising at least one covalently attached ETM; and e) detecting said ETM as an indicator of the presence of said target sequence wherein said RCP further comprises a third domain comprising a capture sequence, and said method further comprises hybridizing said concatamer to a capture probe covalently attached to an electrode (see columns 141, claims 1 and 2).

Regarding claim 1, since Blackburn *et al.*, teach to make a rolling circle concatamer by hybridizing a RCP comprising a first ligation sequence and a capture sequence to a target sequence and ligation and amplification reactions and hybridize said concatamer to a capture probe covalently attached to an electrode (see columns 141, claims 1 and 2), Blackburn *et al.*, disclose a sensor device (ie., an electrode) having a sensing interface carrying capturing oligonucleotides, each having a nucleotide sequence (ie., multiple identical capture probes), a stably hybridizing portion of which is complementary to a first portion (ie., a capture sequence) of the target oligonucleotides (ie., RCP in said concatamer having RCP wherein RCP is the target oligonucleotide here) wherein said sensor device comprises an electrochemical probe carrying the sensing interface (ie., an electrode) and the probe is located in a surrounding medium (ie., the hybridization buffer) as recited in (a) of claim 1, providing verification oligonucleotides, each having a nucleotide sequence (ie., multiple identical target nucleic acids), a stably hybridizing portion of which is complementary to a second portion of the target oligonucleotide (ie., a first ligation sequence of RCP), other than said first portion as recited in (b) of claim 1(c), contacting the sample (ie., said concatamer having RCP) with the sensing interface under conditions such as to allow the target oligonucleotides (ie., RCP in said concatamer) if present in the sample, to hybridize to the capturing oligonucleotides (ie., multiple identical capture probes on the electrode) as recited in (c) of claim 1, and prior to (c), allowing the verification oligonucleotides (ie., multiple identical target sequences) to hybridize to the target oligonucleotides (ie., RCP) if present in the sample as recited in (d) of claim 1. Since Blackburn *et al.*, teach detecting said ETM as an indicator of the presence of said target sequence (see column 141, claim 1) and insulators (such as resistance) is used to monitor electron transfer

between ETM and the electrode (see column 92, fourth paragraph), and the measurement of insulators (such as resistance) must performed in or through the hybridization buffer, Blackburn *et al.*, disclose detecting the presence of said verification oligonucleotides (ie., the target sequence) on the sensing interface by measuring insulation of the sensing interface (ie., surface of the electrode) to interfacial electron transfer between the sensing interface and the surrounding medium (ie., the hybridization buffer) as recited in (e) of claim 1.

Regarding claim 2, Blackburn *et al.*, teach that said detection is based on Faradaic impedance spectroscopy or amperometric measurements (see column 91, last paragraph and columns 92 and 96).

Therefore, Blackburn *et al.*, teach all limitations recited in claims 1 and 2.

13. Claims 23-26, 28, 29, and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Durst *et al.*, (US Patent No. 6,358,752 B1, priority date: May 21, 1998).

Durst *et al.*, teach liposome-enhanced test device and method.

Regarding claims 23 and 24, Durst *et al.*, teach a method for detecting or quantifying an analyte in a liquid test sample comprising: (1) providing a test device comprising: a contact portion on a first absorbent material, a capture portion either on said first absorbent material, or on a second absorbent material in fluid flow contact with said first absorbent material, wherein said capture portion has a first binding material bound to said capture portion, and an electrode array comprising a first conductor having a plurality of fingers, and a second conductor having a plurality of fingers, wherein said fingers of said first conductor are interdigitated with said fingers of said second conductor, said first and second conductors are electrically connected to

one another via a voltage source and readout device, and said array is positioned to induce redox cycling of an electroactive marker released from liposomes which migrate beyond said capture portion; (2) applying the test sample to said contact portion; (3) applying a voltage across said conductors, wherein said potential is sufficient to induce redox cycling of said marker; (4) allowing the test sample to migrate from said contact portion through said capture portion; (5) contacting the test sample with a liposome conjugate of liposomes and a second binding material, wherein said liposomes encapsulate an electroactive marker, wherein said second binding material binds with a portion of the analyte, and wherein said first binding material binds with a portion of the analyte other than the portion of said analyte for which said second binding material is selected; (6) incubating the test sample with the conjugate for a time sufficient to permit reaction between any analyte present in the test sample and the second binding material; (7) after said incubating and said allowing, lysing any liposomes which migrate beyond said capture portion to release said marker, whereby said marker undergoes redox cycling induced by said conductors causing current to flow between said first and second conductors; and (8) detecting the presence or amount of said current and correlating the presence or amount of said current with the presence or amount, respectively, of the analyte in the test sample, wherein the presence or amount of said current is inversely proportional to the presence or amount, respectively, of the analyte in the test sample (see claims 1 and 2 in columns 24-26). Since Durst *et al.*, teach that said analyte is a target nucleic acid molecule, said first binding material is a capture probe selected to at least partially hybridize with a portion of said target nucleic acid molecule, and said second binding material is a reporter nucleic acid molecule selected to at least partially hybridize with a portion of said target nucleic acid molecule other than the portion of

said target nucleic acid molecule for which said capture probe is selected and said array is positioned to induce redox cycling of an electroactive marker released from liposomes which migrate beyond said capture portion (see claims 2 and 6 in columns 25 and 26, lines 4-23 in column 12, and Figure 6), Durst *et al.*, disclose a sensor device comprising an electrochemical probe (ie., an electrode in the electrode array) carrying a sensing interface (ie., the first absorbent material) with a capturing oligonucleotide (ie., the capture probe on said capture portion) as recited in step (a) of claim 23 and claim 24. Since Durst *et al.*, teach contacting the test sample with a liposome conjugate of liposomes and a second binding material, wherein said liposomes encapsulate an electroactive marker, wherein said second binding material (ie., the reporter nucleic acid molecule) binds with a portion of the analyte (ie., target nucleic acid molecule) and wherein said first binding material (ie., the capture probe) binds with a portion of the analyte (ie., target nucleic acid molecule) other than the portion of said analyte for which said second binding material is selected, and incubating the test sample with the conjugate for a time sufficient to permit reaction between any analyte present in the test sample and the second binding material (see claim 2 in column 26, lines 3-23 of column 12 and Figure 6) wherein verification oligonucleotide is the second binding material (ie., a reporter nucleic acid molecule) and a marker-encapsulating liposome is a signal amplifying agent as recited in claim 23 which indirectly binds to the sense interface as recited in step (e) of claim 23, steps (b) to (e) of claim 23 are anticipated by Durst *et al.*. Since Durst *et al.*, teach, after said incubating and said allowing, lysing any liposomes which migrate beyond said capture portion to release said marker, whereby said marker undergoes redox cycling induced by said conductors causing current to flow between said first and second conductors, detecting the presence or amount of

said current and correlating the presence or amount of said current with the presence or amount, respectively, of the analyte (ie., target nucleic acid molecule) in the test sample, wherein the presence or amount of said current is inversely proportional to the presence or amount, respectively, of the analyte in the test sample (see claim 2 in column 26), Durst *et al.*, disclose to detect the presence of said target oligonucleotides and said verification oligonucleotides (ie., the seconding binding material or the reporter nucleic acid) on the sensing interface by detecting of presence of the signal-amplifying agent (ie., a marker-encapsulating liposome) on the sensing interface as recited in step (f) of claim 23.

Regarding claim 25, since Durst *et al.*, teach that induction of redox cycling of the electroactive marker released from the liposomes captured in the capture portion is detected by amperometric detector (see column 18, last paragraph and column 19, first paragraph), claim 25 is anticipated by Durst *et al.*.

Regarding claim 28, since Durst *et al.*, teach that capture and reporter probes are preferably between 17 and 25 nucleotides long, to provide the requisite specificity while avoiding unduly long hybridization times and minimizing the potential for formation of secondary structures under the assay conditions (see column 7, lines 19-40) and the capture and reporter probes are at least partially hybridize with a portion of the target nucleic acid molecule (see column 26, claim 6), claim 28 is anticipated by Durst *et al.*.

Regarding claim 26, since the specification does not define "a microbalance quartz-crystal probe", an electrode in the electrode array is considered as a microbalance quartz-crystal probe as recited in claim 26.

Regarding claim 29, Durst *et al.*, teach that the liposome surface is activated with thiol groups and coupled to a maleimide group on the second binding material (see column 7, third paragraph), Durst *et al.*, disclose that the verification oligonucleotide (ie., the second binding material, a reportor nucleic acid molecule) is conjugated to a recognition agent (ie., a maleimide group) which can specifically bind to said signal-amplifying agent (ie., the marker-encapsulating liposome) as recited in claim 29.

Regarding claim 31, since Durst *et al.*, teach marker-encapsulating liposomes are conjugated with the second binding materials (ie., the reporter nucleic acid molecule) (see columns 24-26, claims 1 and 2, column 12, lines 4-23, and Figure 6), Durst *et al.*, disclose that said verification oligonucleotide (ie., the second binding material) is bound to or complexed with said signal-amplifying agent (ie., marker-encapsulating liposomes).

Therefore, Durst *et al.*, teach all limitations recited in claims 23-26, 28, 29, and 31.

Response to Arguments

I. In pages 14, third paragraph of applicant's arguments, applicant argues that "in Applicants' claimed invention the capturing oligonucleotides are carried on the sensing interface. The Examiner should note that if Durst et al. would place the capturing nucleic acid and the resulting hybridization complex directly on the interdigitated electrode, the redox cycling which is used to measure the analyte would be blocked. Therefore Durst et al. require 2 separate components. Applicants' invention, on the other hand, measures the changes in electron transfer resistance of the electrode. Furthermore, Applicants' methods measure electrostatic repulsion of the oxidized form of the redox label, and not the electrical response of the redox marker released

from the liposomes. Durst et al. do not monitor direct changes in the interfacial properties of the surface as a result of hybridization as in the method of the invention.".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, according to dictionary, interface is defined as "a surface forming a common boundary of two bodies, spaces, or phases" (see attachment). Since Durst *et al.,* teach that the first binding material (ie., a capture probe) is bound to the absorbent material and the test device taught by Durst *et al.,* comprises a contact portion on a first absorbent material, a capture portion on said first absorbent material wherein said capture portion has a first binding material bound to said capture portion, and an electrode array and the absorbent material is located between the electrode array and a marked encapsulating liposome conjugated a second binding material (ie., a reporter nucleic acid molecule) (see columns 7, 8, and 12, columns 24-26, claims 1, 2, and 6, and Figure 6), Durst *et al.,* teach that capturing oligonucleotides (ie., the first binding material) are carried on the sensing interface (ie., the first absorbent material). Second, the claims do not require that the capturing nucleic acid and the resulting hybridization complex are directly on the interdigitated electrode, measurement of electrostatic repulsion of the oxidized form of the redox label, and monitoring direct changes in the interfacial properties of the surface as a result of hybridization as argued by applicant. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

II. In page 14, fourth paragraph of applicant's remarks, applicant argues that "[W]ith respect to claims 3 and 28, Durst et al. teach probes which are between 17 and 25 nucleotides long, while claims 3 and 28 teach oligonucleotides of about 12 nucleotides.".

This argument has been fully considered and the rejection on claim 3 has been withdrawn in view of the amendment filed on April 5, 2004. However, it is not persuasive toward the withdrawal of the rejection on claim 28. Since the capture and reporter probes are at least partially hybridize with a portion of the target nucleic acid molecule (see column 26, claim 6) (ie., including fully hybridize with a portion of the target nucleic acid molecule) and claim 28 does not requires that the stably hybridizing portion of the capturing and verification oligonucleotides is exactly 12 nucleotides, 17 nucleotides is considered as "about 12 nucleotides".

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Blackburn *et al.*, (January 29, 1998) as applied to claims 1 and 2 above, and further in view of Lizardi *et al.*, (US Patent NO. 6,143, 495, filed on November 21, 1996).

The teachings of Blackburn *et al.*, have been summarized previously, *supra.* Blackburn *et al.*, teach that the size of RCP is designed such that it hybridizes "smoothly" to many capture probes on a surface (see column 25, lines 33-37).

Blackburn *et al.*, do not disclose that the stably hybridizing portion of the capturing and verification oligonucleotides is of about 12 nucleotides as recited in claim 3.

Lizardi *et al.*, teach that a region in a detection tag with 10-35 nucleotides forms a specific and stable hybridization complex with a detection probe (see column 10, second paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 3 wherein the stably hybridizing portion of the capturing and verification oligonucleotides is of about 12 nucleotides in view of patents of Blackburn *et al.*, and Lizardi *et al.* One having ordinary skill in the art has been motivated to do so because optimization of the stably hybridizing portion of the capturing and verification oligonucleotides in order to form a specific and stable hybridization complex with their target nucleic acids, in the absence of convincing evidence to the contrary, would have been obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to design the capturing and verification oligonucleotides wherein their stably hybridizing portions are about 12 nucleotides so that

such that it hybridizes "smoothly" to many capture probes on a surface a specific and stable hybridization complex with their target nucleic acids would be formed. More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Where the general conditions of a claim are disclosed in the prior art, it is not inventive, in the absence of an unexpected result, to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (MPEP 2144.05).

16. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Durst *et al.*, (May 21, 1998) as applied to claims 23-26, 28, 29, and 31 above, and further in view of Okahata *et al.*, (Anal. Chem., 70, 1288-1298, April 1, 1998).

The teachings of Durst *et al.*, have been summarized previously, *supra.*

Durst *et al.*, do not disclose to detect the presence of said signal-amplifying agent on the sensing interface using microgravimetric quartz-crystal microbalance analysis as recited in claim 27.

Okahata *et al.*, teach to measure DNA hybridization using microgravimetric quartz crystal microbalance analysis wherein an oligonucleotide probe is immobilized on a 27-MHz quartz crystal microbalance (see pages 1288, 1289, 1290, and 1291).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have immobilized the capturing oligonucleotide recited in claim 23 on a 27-MHz quartz crystal microbalance and detected the target oligonucleotides recited in claim 1 using microgravimetric quartz crystal microbalance analysis in view of the

prior art of Durst *et al.*, and Okahata *et al.*. One having ordinary skill in the art would have been motivated to do so because Okahata *et al.*, have successfully used microgravimetric quartz crystal microbalance analysis to detect DNA hybridization and the simple replacement of one well known detection system (i.e., detecting the presence or amount of the current taught by Durst *et al.*,) from another well known detection system (i.e., microgravimetric quartz crystal microbalance analysis taught by Okahata *et al..*,) during the process of performing the method recited in claim 1 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.6, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 15, third to fifth paragraphs of applicant's remarks, applicant argues that "[O]kahata does not disclose measuring electrostatic repulsion of the oxidized form of the redox label, nor monitoring direct changes in the interfacial properties of the surface as a result of hybridization as in the method of Applicants' invention and therefore does not remedy the deficiencies of Durst et al.".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because the claims do not require "measuring electrostatic repulsion of the oxidized form of the redox label, nor monitoring direct changes in the interfacial properties of the surface as a result of hybridization" as argued by applicant. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

17. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Durst *et al.*, (May 21, 1998) as applied to claims 23-26, 28, 29, and 31 above, and further in view of Pease *et al.*, (US Patent No. 5,618,732, published on April 8, 1997) and Lanza *et al.*, (US Patent No. 5,612,057, published on March 18, 1997).

The teachings of Durst *et al.*, have been summarized previously, *supra.* Durst *et al.*, teach that the liposome (ie., said signal amplifying agent) surface is activated with thiol groups and coupled to a maleimide group (ie., said recognition agent) on the second binding material. Or, conversely, maleimide-activated liposomes and thiol group-activated binding material is employed (see column 7, third paragraph).

Durst *et al.*, do not disclose that said recognition agent is biotin and said signal amplifying agent comprises avidin as recited in claim 30.

Pease *et al.*, teach that thiol group, maleimide group and biotin can be used on liposome surface and these groups are exchangeable. When biotin is used on the liposome surface, the molecule that binds to the liposome surface must be labeled with avidin (see column 28, lines 53-61).

Lanza *et al.*, teach that lipsome is conjugated with avidin and binds to a ligand labeled with biotin (see column 6, lines 31-43).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 30 wherein said recognition agent is biotin and said signal amplifying agent (ie., liposome) comprises avidin in view of the patents of Durst *et al.*, Pease *et al.*, and Lenza *et al.*. One having ordinary skill in the art would have been motivated to do so because Pease *et al.*, and Lenza *et al.*, have successfully used biotin/avidin system to bind liposome to its ligand and the simple replacement of one well known binding system (i.e., maleimide/ thiol taught by Durst *et al.*,) from another well known binding system (i.e., the biotin/avidin taught by Lemar *et al.*,) during the process of performing the method recited in claim 30 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.6, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Claims 32 and 33 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

19. No claim is allowed.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703)872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
August 5, 2004

FRANK LU
PATENT EXAMINER